Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name:	Quillivant XR® (methylphenidate hydrochloride) powder for suspension
Pediatric Labeling Approval Date:	September 27, 2012
Application Type/Number:	NDA 202100
Applicant/Sponsor:	NextWave Pharmaceuticals, Inc
OSE RCM #:	2014-1562

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse events reports and drug utilization data for Quillivant XR® (methylphenidate hydrochloride powder for suspension) in pediatric patients.

Quillivant XR® was first approved in 2012 and is indicated for Attention Deficit Hyperactivity Disorder (ADHD). The approved pediatric labeling is for ADHD in patients aged 6-17 years. The drug utilization data identified that the vast majority of patients who received a dispensed prescription for Quillivant XR® from outpatient retail pharmacies were pediatric patients aged 0-16 years, primarily pediatric patients aged 6-11 years. Pediatricians were the top prescribing specialty, while "Attention Deficit Disorder" was the only diagnosis associated with Quillivant XR®.

The Division of Pharmacovigilance (DPV) searched the FDA Adverse Event Reporting System (FAERS) database for reports received from September 27, 2012 (FDA approval date of Quillivant XR®) through July 31, 2014. This review focused on all serious pediatric adverse events spontaneously reported with Quillivant XR®. Of the 23 cases reviewed in pediatric patients, there were no new safety signals identified, no apparent increased severity or frequency of labeled adverse events, and no deaths associated with Quillivant XR®.

There is no evidence from these data that there are new pediatric safety concerns with Quillivant XR® at this time. DPV will continue routine pharmacovigilance monitoring for Quillivant XR®.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Product Information and Dosing[1]
Quillivant XR® (methylphenidate hydrochloride) powder for suspension was approved on September 27, 2012. It is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Quillivant XR® contains approximately 20% immediate-release and 80% extended-release methylphenidate. After reconstitution with water, the suspension contains 5 mg/mL of methylphenidate. For patients 6 years and above, the recommended starting dose of Quillivant XR® is 20 mg once daily in the morning. The dose may be titrated weekly in 10 mg to 20 mg increments up to a maximum dose of 60 mg daily.

Pediatric Use
The following information is verbatim from the Prescribing Information of Quillivant XR®[1]:
"The safety and effectiveness of QUILLIVANT XR *have been established in pediatric patients ages 6 to 17 years. Use of* QUILLIVANT XR *in pediatric patients 6 to 12 years of age is supported by adequate and well-controlled studies. Use in 12 to 17 year olds is supported by the adequate and well-controlled studies of* QUILLIVANT XR *in younger pediatric patients and additional pharmacokinetic data in adolescents, along with safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established. Safety and efficacy in pediatric patients below the age of 6 years have not been established."*

Clinical Study
The following information is verbatim from the Prescribing Information of Quillivant XR®[1]:
"The efficacy of QUILLIVANT XR *was evaluated in a laboratory classroom study conducted in 45 pediatric patients (ages 6 to 12 years) with ADHD. The study began with an open-label dose optimization period (4 to 6 weeks) with an initial* QUILLIVANT XR *dose of 20 mg once daily in the morning. The dose could be titrated weekly in increments of 10 or 20 mg until an optimal dose or the maximum dose of 60 mg/day was reached. Subjects then entered a 2-week randomized, double-blind, crossover treatment with the individually optimized dose of QUILLIVANT* XR *or placebo. At the end of each week, school teachers and raters evaluated the attention and behavior of the subjects in a laboratory classroom using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. The primary efficacy endpoint was the SKAMP-Combined score at 4 hours post-dosing. The key secondary efficacy endpoints were the SKAMP-Combined scores at 0.75, 2, 8, 10, and 12 hours post-dosing.*
SKAMP-Combined scores were statistically significantly lower (improved) at all time points (0.75, 2, 4, 8, 10, 12 hours) post-dosing with QUILLIVANT XR *compared to placebo."*

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The following information is from the Highlights of Prescribing Information[1]:

- **BOXED WARNING**
  - WARNING: ABUSE AND DEPENDENCE
    CNS stimulants, including QUILLIVANT XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

- **CONTRAINDICATIONS**
  - Known hypersensitivity to methylphenidate or product components
  - Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days

- **WARNINGS AND PRECAUTIONS**
  - *Serious Cardiovascular Reactions*: Sudden death has been reported in association with CNS stimulants at recommended doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease
  - *Blood Pressure and Heart Rate Increases*: Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic.
  - *Psychiatric Adverse Reactions*: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to QUILLIVANT XR use.
  - *Priapism*: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms or prolonged penile erections or priapism are observed
  - *Peripheral Vasculopathy, including Raynaud's Phenomenon*: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants
  - *Long-Term Suppression of Growth*: Monitor height and weight at appropriate intervals in pediatric patients.

- **ADVERSE REACTIONS**
  - Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight

decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased.

- **USE IN SPECIFIC POPULATIONS**
  - Pregnancy: Based on animal data, may cause fetal harm.
  - Nursing Mothers: Discontinue drug or discontinue nursing, taking into consideration the importance of the drug to the mother.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

2.1.1 Determining Settings of Care

Proprietary drug utilization databases were used to conduct this analysis.

The IMS Health, IMS National Sales Perspectives™ data (see **Appendix A** for full database descriptions) were used to determine various settings of care to which Quillivant XR® (methylphenidate) was sold. During year 2013, the sale of Quillivant XR® by number of bottles sold from the manufacturer indicated that approximately 95% was distributed to the outpatient retail pharmacy settings, 5% to the non-retail pharmacy setting, and <1% to the mail-order/specialty pharmacies.[2] As a result, outpatient retail pharmacy utilization patterns were examined. Mail-order/specialty pharmacies and non-retail settings data were not included in this analysis.

2.1.2 Data Sources Used

The IMS, Total Patient Tracker (TPT) database was used to obtain the nationally estimated number of patients receiving a dispensed retail prescription for Quillivant XR® in the U.S., stratified by patient age (0-16 years old and 17 years and older), from September 2012 through June 2014. The IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of dispensed retail prescriptions for Quillivant XR® in the U.S., stratified by prescriber specialty, from September 2012 through June 2014, cumulative. Encuity Research, LLC., Treatment Answers™ was used to obtain the diagnoses associated with the use of Quillivant XR®, stratified by patient age (0-16 years old and 17 years and older) for the aggregate time period from September 2012 through June 2014.

2.2 RESULTS

Table 2.2.1 provides the nationally estimated number of patients who received a dispensed prescription for Quillivant XR® from U.S. outpatient retail pharmacies, stratified by patient age from September 2012 through June 2014, cumulative. Approximately 72,000 patients received a dispensed prescription for Quillivant XR® over the cumulative time. The vast majority of patients who received a dispensed prescription for Quillivant XR® were pediatric patients aged 0-16 years who accounted for nearly 94% (68,000 patients), while patients aged 17 years and older accounted for approximately 6% of total patients. Among

the pediatric patients, approximately 75% (51,000 patients) were aged 6-11 years,15% (10,000 patients) were aged 2-5 years, 14% (9,700 patients) were aged 12-16 years, and <0.1% of pediatric patients were aged 0-1 years.

Table 2.2.1

Nationally Estimated Number of Patients Who Received a Dispensed Prescription for Quillivant XR® Statified by Patient Age, Dispensed Through U.S. Outpatient Retail Pharmacies, September 2012-June 2014

	September 2012-June 2014	
	Total	
	Patients (N)	% Share
Quillivant XR®	72,282	*100.0%*
0-16 years	67,801	*93.8%*
0-1 years	21	*<0.1%*
2-5 years	10,062	*14.8%*
6-11 years	50,835	*75.0%*
12-16 years	9,724	*14.3%*
17+ Years	4,626	*6.4%*
Unknown Age	93	*0.1%*

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period , patients may be counted more than once in the individual age categories. For this reason, summing across age groups is not advisable and will result in overestimates of patient counts.

IMS Health: Total Patient Tracker (TPT). Sept. 2012 through Jun. 2014. Extracted Oct. 2014. File: TPT 2014-1562 Quillivant BPCA.xls

2.2.2 Dispensed Prescriptions for Quillivant XR® by Prescriber Specialty

(Table 2.2.2) Approximately 237,000 prescriptions were dispensed for Quillivant XR® during the cumulative time period from September 2012 through June 2014. Pediatrics was the top prescribing specialty with approximately 49.5% (117,000 prescriptions) of the total number of dispensed prescriptions for Quillivant XR®, followed by psychiatry with 23% (55,000 prescriptions) and nurse practitioner with 9% (21,000 prescriptions).

Table 2.2.2

Nationally estimated number of Quillivant XR (methylphenidate) prescriptions dispensed from U.S. Outpatient retail phatmacies, stratified by prescriber specialty from September 2012-June 2014, cumulative

	September 2012 - June 2014	
	Total Rxs (N)	**% Share**
QUILLIVANT XR	237,033	*100.0%*
PEDIATRICS	117,429	*49.5%*
PSYCHIATRY	54,664	*23.1%*
NURSE PRACTITIONER	21,271	*9.0%*
OSTEOPATHIC MEDICINE	12,468	*5.3%*
NEUROLOGY	10,080	*4.3%*
FAMILY PRACTICE	8,533	*3.6%*
PHYSICIAN ASSISTANT	4,353	*1.8%*
SPECIALTY UNSPECIFIED	2,040	*0.9%*
INTERNAL MEDICINE	1,852	*0.8%*
INTERNAL MED/PEDIATRICS	1,237	*0.5%*
All Others	3,106	*1.3%*

IMS Health: National Prescription Audit (NPA). Sept 2012 through Jun. 2014. Extracted Oct. 2014. File: NPA & Specialty 2014-1562 Quillivant BPCA.xlsx

2.2.3 Diagnosis Associated with Quillivant XR®

Table 2.2.3 shows the diagnoses, in terms of drug use mentions[a], associated with the use of Quillivant XR®, stratified by patient age (0-16 years old and 17 years and older), as reported by office-based physician practices for the cumulative time period from September 2012 through June 2014. Diagnoses were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied to the estimates. There were a total of 70,000 drug use mentions for Quillivant XR® captured during the cumulative time period. Pediatric patients aged 0-16 years accounted for 49,000 (95% CI 15,000-84,000) drug use mentions with “Attention Deficit Disorder” (ICD-9 code 314.0) as the only diagnosis captured. Among patients aged 17 years and older, “Attention Deficit Disorder” ICD-9 code 314.0 was also the only diagnosis associated with Quillivant XR® with approximately 5,000 drug use mentions (95% C.I. <500-15,000) of the total drug use mentions during the cumulative time period.

[a] "Drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Table 2.2.3

Top Diagnoses Associated with the Use of Quillivant XR® as reported by U.S. Office-Based Physician Surveys, from September 2012 to June 2014, Cumulative

	September 2012 to June 2014		
	Uses (N)	Share (%)	95% Confidence Interval
Quillivant XR® Total Use	70,000	*100.0%*	29,000 - 111,000
0-16 Years	49,000	*70.4%*	15,000 - 84,000
3140 ATTENTION DEFICIT DIS	49,000	*100.0%*	15,000 - 84,000
17+ Years	5,000	*6.5%*	<500 - 15,000
3140 ATTENTION DEFICIT DIS	5,000	*100.0%*	<500 - 15,000
Unspecified	16,000	*23.2%*	<500 - 36,000
3140 ATTENTION DEFICIT DIS	16,000	*100.0%*	<500 - 36,000

Source: Encuity Research, LLC, Treatment Answers (TM). September 2012 - July 2014 Extracted October 2014. File: Enquity 2014-Quillivant XR BPCA

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FAERS Search Strategy

The FAERS database was searched with the strategy described in **Table 3.1.1**. See **Appendix B** for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy	
Date of search	September 19, 2014
Time period of search	September 27, 2012* - July 31, 2014
Product Name(s)	Quillivant XR
Search Parameters	All ages, all outcomes, worldwide

* *FDA approval date of Quillivant XR®*

3.2 RESULTS

3.2.1 Total number of FAERS cases by Age

Table 3.2.1 Total Adult and pediatric FAERS cases (From September 27, 2012 to July 31, 2014) with Quillivant XR®*

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	28 (28)	12 (12)	7 (7)
Pediatrics (0 - <17 years)	156 (155)	32‡ (31)	2§ (2)

** May include duplicates and transplacental exposures, and have not been assessed for causality*

† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

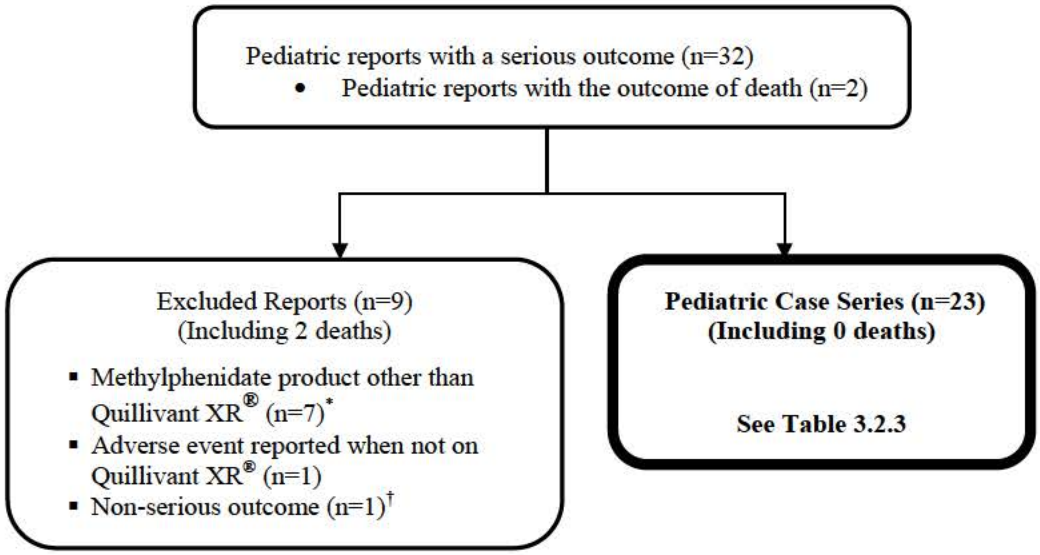
‡ See Figure 3.2.2

§ No additional cases of pediatric deaths were identified among cases not reporting an age.

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 32 pediatric reports with a serious outcome (See **Table 3.2.1**). **Figure 3.2.2** below depicts the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Quillivant XR®



* First death case: Literature report of a 14-year old male who died of intentional overdose of bupropion, clonidine, and methylphenidate (not Quillivant XR®).

† Second death case: DPV followed up with the reporter who stated that death was reported in error. The case was corrected to a non-serious outcome.

3.2.3 *Characteristics of Pediatric Case Series*

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with Quillivant XR® (N=23)

Age	0 - < 1 month	0
	1 month - <2 years	0
	2- < 6 years	7
	6- <12 years	14
	12- < 17 years	2
Sex	Male	18
	Female	5
Country of reporter	United States	23
Reported Indication	ADHD	18
	Unknown	5
Serious Outcome*	Hospitalized	6
	Other serious	17

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

3.3 SUMMARY OF SERIOUS ADVERSE EVENT REPORTS (N=23)

Cases in this section are categorized by the Preferred Terms or concepts that best represent the reported adverse event(s). Preferred Terms are then grouped by like terms and organized by System Organ Class.

3.3.1 *Psychiatric disorders (N=7)*

Agitation (n=1): labeled in *Adverse Reactions* and *Overdose* sections.
Case #9870930: A 5-year-old male was initiated on Quillivant XR® 10 mg daily for ADHD. On the next day, the patient was "agitated and uncontrollable", for which he was hospitalized for two days. Quillivant XR® was discontinued. The treatment and clinical outcome were not provided.

Homicidal ideation (n=1): labeled in *Drug Abuse and Dependence* section.
Case #9336912: A 6-year-old male was "homicidal" while on Quillivant XR®. Methylphenidate was discontinued for two weeks then restarted. Upon resumption of the medication, the patient did not experience further homicidal ideation.

Psychotic disorder (n=1): labeled in *Warnings and Precautions* section.
Case #9565110: A 7-year-old female was taking Quillivant XR® (dose unknown). Her medical history and concomitant medication (if any) were not provided. The patient experienced a "psychotic event" (cried, screamed uncontrollably, and said "weird things"). She also refused to eat for nine hours. The clinical outcome was unknown.

Visual hallucination (n=1): labeled in *Adverse Reactions* section.
Case #9508350: An 8-year-old male was on Quillivant XR® (dose unknown). He experienced hallucinations (saw bugs and frogs). No further information was provided.

Anger (n=1): unlabeled
Case #9773337: A 6-year-old male was prescribed Quillivant XR® 5 mg daily for ADHD. After the dose was increased to 10 mg daily, the patient became "angry and violent". Consequently, the methylphenidate dose was decreased back to 5 mg daily, and the medication was eventually discontinued as the anger and violent behaviors did not resolve. The physician correlated the events to Quillivant XR®; however, he stated that the patient's behavior was attributed to methylphenidate in general (not specific to the brand product).
Reviewer's comment: Anger is labeled in the Adverse Reactions section of the Concerta® (methylphenidate extended-release) label.

Autism (n=1): unlabeled
Case #9262978: A 5-year-old male was on Quillivant XR® since an unknown date. He was previously on methylphenidate transdermal patch. No information on his medical history or concomitant medication (if any) was provided. The patient's mother reported that he is autistic.
Reviewer's comment: This case lacks sufficient information to make an assessment. In addition, the background rates of autism and ADHD in this age group is relatively high, and it is not uncommon for patients to have comorbid features of ADHD and autism.

Obsessive-compulsive disorder, onychophagia (n=1): unlabeled
Case #10155589: A 5-year-old male started on Quillivant XR® 10 mg daily on February 26, 2014. His medical history included nasal allergies. He was not on any other medication. Sixteen days after starting Quillivant XR®, the patient was chewing and biting his fingers and toes. By the following month, he had "no pads on ends of fingers" and he was seen in the emergency department. The reporter, a nurse, considered this case to be serious due to a possible infection. An antibiotic ointment was prescribed as treatment. Quillivant XR® was discontinued, and the patient recovered.
Reviewer's comment: From the information provided, there is a temporal relationship and positive dechallenge to associate a possible causal relationship between Quillivant XR® and nail biting. Habitual nail biting is common in children and could be considered in the obsessive-compulsive spectrum disorder. Obsessive-compulsive disorder commonly co-occurs with other psychiatric disorders such as ADHD or anxiety.[3,4]

3.3.2 *Injury, poisoning and procedural complications (N=3)*

Medication error (n=3): unlabeled

10 mL of Quillivant XR® instead of the prescribed dose of 10 mg (2 mL). Two days later, the patient went to the emergency department due to agitation, tachycardia, insomnia, and loss of appetite. The patient was discharged home on the same day with methylphenidate on hold. After two days, Quillivant XR® was restarted at the correct dose of 10 mg.

Case #10254676: A 9-year-old female was initiated on Quillivant XR®. The medication was dispensed from the pharmacy without reconstitution with water. The patient's parent reconstituted Quillivant XR® with an incorrect amount of water, thus the patient received an incorrect dose. The patient was admitted to the hospital for supportive therapy and observation.

Case #10283665: A 4-year-old male with ADHD was given 25 mg (5 mL) of Quillivant XR® instead of the prescribed dose of 5 mg (1 mL). The patient's mother saw the strength of 25 mg/5 mL on the label of the Quillivant XR® bottle; she mistakenly gave 5 mL to the patient. The patient's mother called the pediatrician's office to report "random arm movements" and "strange movements of mouth and tongue" after the first dose of Quillivant XR®. The poison control center recommended the administration of diphenhydramine and close observation. The patient was later seen at the pediatrician's office where he presented with continued involuntary movements, rapid speech, and being "hot" and "sweaty". He was admitted to the hospital in the intensive care unit for observation of the dystonic reaction. The patient returned to baseline after five hours in the hospital, and he was discharged home.

Reviewer's comment: Three medication errors, which led to hospitalization, were identified in this review. On October 9, 2014, the Division of Medication Error Prevention and Analysis (DMEPA) conducted a review on medication errors related to Quillivant XR®.[5] *This review identified 17 cases of medication errors such as wrong technique, wrong storage, improper dose, and wrong quantity dispensed. DMEPA's recommendations for potential improvements to the carton labeling to decrease wrong technique errors and wrong storage errors are outlined in their review.*

3.3.3 *Cardiac disorders (N=3)*

Blood pressure increased, tachycardia (n=1): labeled in *Warnings and Precautions* section.

Case #9611689: A 6-year-old male was on Quillivant XR® and guanfacine (Tenex®). The patient experienced hypertension and tachycardia on the same day that methylphenidate started. Guanfacine had been discontinued on an unspecified date in the same month prior to the event. Due to the hypertension and tachycardia, the patient was taken to the emergency department. Treatment was not specified, but it was reported that the patient would restart guanfacine. At the time of the report, methylphenidate was discontinued, and the case did not report a plan for its resumption.

Palpitations (n=1): labeled in *Adverse Reactions* section
Case #10342155: A 15-year-old female was on Quillivant XR® 20 mg daily for ADHD. Her medical history included anxiety and drug hypersensitivity to an unspecified antidepressant. Her concomitant medications were unknown. While on Quillivant XR®, she had mood swings, worsening headaches, no appetite, and palpitations. After five days of taking Quillivant XR®, she was hospitalized due to the palpitations. Methylphenidate was discontinued. Clinical outcome was unknown.

Syncope (n=1): labeled in *Warnings and Precautions* section. (Section 5.2 Serious Cardiovascular Reactions – "Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with QUILLIVANT XR.")
Case #9275773: An 11-year-old female was started on Quillivant XR®. Her medical history included "psychological issues". While on methylphenidate, the patient experienced syncope, felt "pressure in chest and neck", and "woke up on the floor". No further information was provided.

3.3.4 *Eye disorders (N=2)*

Vision blurred, mydriasis (n=1): labeled in *Adverse Reactions* section.
Case #9216689: A 6-year-old male started Quillivant XR® 20 mg daily. The patient experienced blurred vision on the same day and was seen in the emergency department. His pupils were "severely dilated". Quillivant XR® was discontinued.

Anisometropia, amblyopia, strabismus (n=1): unlabeled
Case #9338353: A 6-year-old male was on Quillivant XR® 25 mg twice daily. His past medical history included vision problem (vision of 20/30) and ADHD. About four months after the initiation of methylphenidate, his vision worsened (vision became 20/100), and he was diagnosed with anisometropic amblyopia and strabismus. The patient did not recover. The reporting physician stated there was a low possibility that the events were related to Quillivant XR®.
Reviewer's comment: The patient had pre-existing vision impairment.

3.3.5 *Immune system disorders (N=2)*

Rash generalised (n=1): labeled in *Adverse Reactions* section.
Case #9371702: A 4-year-old male was on Quillivant XR® 10 mg daily for ADHD. After the first dose of methylphenidate, the patient experienced a truncal rash. The rash spread to the full body after the second dose of the medication. Treatment information was not reported, but the rashes resolved after methylphenidate was discontinued.

Swollen tongue, pharyngeal oedema (n=1): labeled in *Contraindications* and *Adverse Reactions* section as hypersensitivity reactions.
Case #103332976: A 6-year-old female with autism, heartburn, and ADHD was started on an unknown dose of Quillivant XR®. The patient's medical history also included an allergic reaction to an unknown medication. Her concomitant

medication included omeprazole for heartburn. She experienced swelling of the tongue and throat on an unspecified date. Diphenhydramine was given and methylphenidate was discontinued. Upon follow-up, the nurse reported that she did not believe the reaction was due to methylphenidate.

3.3.6 *Nervous system disorders (N=2)*

Tic (n=2): labeled in *Adverse Reactions* section.
Case #9286330: A 5-year-old male was on Quillivant XR® 10 mg daily for ADHD then the dose was decreased to 5 mg daily on an unknown date. The patient's past medical history and concomitant medication (if any) were not reported. While on methylphenidate, the patient experienced "facial tics, tongue rolling, and squinting eyes". Due to the adverse events, Quillivant XR® was discontinued and atomoxetine was initiated for ADHD.

Case #9464488: A 7-year-old male started on Quillivant XR® 30 mg daily for ADHD. The patient was previously on lisdexamfetamine which stopped two months prior to the initiation of Quillivant XR® and methylphenidate transdermal patch on an unknown date. Adverse reactions while on methylphenidate included weight loss, abdominal pain, nausea, tachycardia, memory loss, and acted "like a zombie". The patient had tics in which his grandmother described that they resembled a seizure (eyelids were rapidly moving, legs "vibrating", and hands "going everywhere"). The patient also had mood swings and an unresponsive attitude.

3.3.7 *Gastrointestinal disorders (N=1)*

Melaena (n=1): unlabeled
Case #9779909: A consumer reported that her 9-year-old son had "black tarry stools" while on Quillivant XR®. No further information was provided.
Reviewer's comment: Not enough information was provided (i.e. medical history, time to event onset, diagnosis, clinical outcome) to associate the adverse event with methylphenidate.

3.3.8 *Respiratory, thoracic and mediastinal disorders (N=1)*

Respiratory depression (n=1): unlabeled
Case #9493478: A 5-year-old male started Quillivant XR® 20 mg daily for ADHD. The patient's medical history was not provided. Concomitant medications included clonidine, montelukast, and desmopressin nasal spray. Two days after Quillivant XR® started, the patient experienced "respiratory depression/respiratory distress". He was admitted to the hospital and required intubation. The patient also had vomiting, altered mental status, and seizure. The patient recovered and methylphenidate was permanently discontinued.
Reviewer's comment: The patient's medical history was not provided; as the patient was on montelukast, it is unclear if the patient had underlying asthma (or whether the montelukast was used for rhinitis). With the limited information provided, it is challenging to determine methylphenidate's role in the adverse events.

3.3.9 *Vascular disorders (N=1)*

Haemorrhage, contusion, wound (n=1): unlabeled
Case #9771067: A 7-year-old male started on Quillivant XR® with the dose titrated to 30 mg daily. He was not on any concomitant medications. About four days after the initiation of Quillivant XR®, the patient had bruises without local trauma. The patient's mother also reported that the medication did not work. On an unspecified date, the dose of Quillivant XR® was increased to an unknown dose twice daily. About five months after the initiation of Quillivant XR®, a big bruise appeared on his leg and opened up; the wound bled and scabbed. His hematology laboratory results were within normal limits.
Reviewer's comment: Thrombocytopenia is a labeled event for methylphenidate but in this case, the patient's platelet count was normal. An alternative etiology for the bruising and unusual bleeding cannot be ruled out.

3.3.10 *General disorders and administration site conditions (N=1)*

Drug effect incomplete (n=1): unlabeled
Case #10311043: A 16-year old male was on Quillivant XR® 30 mg daily. The patient's medical history included a congenital "disability" and ADHD. His concomitant medications included clonidine, quetiapine, and guanfacine extended-release. About two months after the initiation of Quillivant XR®, the patient's mother reported that the patient became aggressive when the methylphenidate wore off in the afternoon. Subsequently, the dose of Quillivant XR® was increased to 40 mg daily. The consequent outcome from the dosage increase was unknown. The manufacturer investigated the product quality complaint; all results were found to be within specifications.
Reviewer's comment: DPV completed a 915 non- New Molecular Entity safety review in October 2014, which identified a potential lack of effect issue (e.g. drug ineffective, drug wearing off too quickly) with Quillivant XR® that warrants further evaluation.[6]

3.4 SUMMARY OF PEDIATRIC DEATHS (N=0)

There were no pediatric deaths associated with Quillivant XR® identified in this review.

4 DISCUSSION

This review focused on serious pediatric adverse events spontaneously reported with Quillivant XR®. Among the 23 cases reviewed, DPV identified a total of ten cases with an unlabeled event. Three cases reported a medication error; DMEPA examined this issue and completed a review in October 2014. One case reported drug effect incomplete. The Division of Psychiatry Products is currently investigating a possible lack of effect issue with Quillivant XR®. The remaining six cases were single cases of adverse events across various System Organ Classes; the majority of these cases provided limited details for assessment. Overall, there were no new safety signals identified, no apparent increased severity or frequency of labeled adverse events, and no deaths associated with Quillivant XR®.

The drug utilization data identified that the vast majority of patients who received a dispensed prescription for Quillivant XR® from outpatient retail pharmacies were pediatric patients aged 0-16 years, primarily pediatric patients aged 6-11 years. Pediatricians were the top prescribing specialty, while “Attention Deficit Disorder” was the only diagnosis associated with Quillivant XR®.

5 CONCLUSION

There is no evidence from these data that there are new pediatric safety concerns with Quillivant XR® at this time.

6 RECOMMENDATIONS

DPV will continue routine pharmacovigilance monitoring for Quillivant XR®.

7 REFERENCES

1. Quillivant XR [package insert]. New York; NY: Pfizer, Inc; December 2013.
2. IMS Health, National Sales Perspectives™ Data Extracted October 2014. File: NSP 2014-1562 Quillivant BPCA.xlsx
3. Pacan P, Grzesiak M, Reich A, Szepietowski JC. Onychophagia as a spectrum of obsessive-compulsive disorder. Acta Derm Venereol. 2009;89(3):278-80.
4. Rosenberg D. Obsessive-compulsive disorder in children and adolescents: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on November 4, 2014.)
5. Brahmbhatt M. FDA Post Marketing Medication Error Review – Quillivant XR. October 9, 2014.
6. Suggs C, Ritter M. FDAAA Section 915 non-New Molecular Entity (non-NME) Postmarket Safety Summary – Quillivant XR. October 6, 2014.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased through these channels of distribution may be a possible surrogate for use, assuming facilities purchase drugs in quantities reflective of actual patient use.

IMS, National Prescription Audit

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 80% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are available on-line for 72- rolling months with a lag of 1 month.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Encuity Research, LLC., TreatmentAnswers™

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS

FAERS Case Number	Version Number	Manufacturer Control Number
9216689	1	US-PFIZER INC-2013109925
9262978	1	US-PFIZER INC-2013131636
9275773	1	US-PFIZER INC-2013138811
9286330	1	US-PFIZER INC-2013145285
9336912	1	US-PFIZER INC-2013172747
9338353	2	US-PFIZER INC-2013174249
9371702	1	US-PFIZER INC-2013190527
9464488	1	US-PFIZER INC-2013239020
9493478	2	US-PFIZER INC-2013252330
9508350	1	US-PFIZER INC-2013257731
9565110	1	US-PFIZER INC-2013277446
9611689	1	US-PFIZER INC-2013290651
9771067	3	US-PFIZER INC-2013361696
9773337	1	US-PFIZER INC-2013364271
9779909	1	US-PFIZER INC-2013365482
9870930	1	US-PFIZER INC-2014031018
10051384	2	US-PFIZER INC-2014091658
10155589	2	US-PFIZER INC-2014123019
10254676	1	
10283665	1	
10311043	2	US-PFIZER INC-2014199029
10332976	2	US-PFIZER INC-2014204825
10342155	1	US-PFIZER INC-2014207699

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